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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/714,852	11/18/2003	Hidenobu Senpuku	245617US0	3710

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EXAMINER	
KAPUSHOC, STEPHEN THOMAS	
ART UNIT	**PAPER NUMBER**
1634	

NOTIFICATION DATE	DELIVERY MODE
09/11/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/714,852	SENPUKU ET AL.	
	Examiner	Art Unit	
	Stephen Kapushoc	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 June 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 2 and 3 are cancelled.
Claim 1 is pending and examined on the merits.

Please note: The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/26/2007 has been entered.

This Office Action is in reply to Applicants' correspondence of 6/26/2007. Claim(s) 2 and 3 is/are cancelled; no claim(s) is/are withdrawn; no claim(s) has/have been newly added; claim(s) 1 has/have been amended.

Applicants' remarks and amendments have been fully and carefully considered but are not found to be sufficient to put this application in condition for allowance. Any new grounds of rejection presented in this Office Action are necessitated by Applicants' amendments. Any rejections or objections not reiterated herein have been withdrawn in light of the amendments to the claims or as discussed in this Office Action.

This Action is **NON-FINAL**.

Withdrawn Claim Rejections - 35 USC § 112 2nd ¶ - Indefiniteness

1. The rejections of claims under 35 USC 112 2nd ¶ for indefiniteness as presented in the previous Office Action are withdrawn in light of the amendments to claim 1 and the cancellation of claim 3.

New Claim Rejections - 35 USC § 112 2nd ¶ - Indefiniteness

2. Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is unclear over recitation of the limitation that a table 'correlates a combination of two different genotypes or combinations of the same genotype and caries risk'. In the analysis of human genetic polymorphic content, the content at a particular locus on one chromosomes is termed an 'allele', and the content at the locus on both chromosomes is termed a 'genotype'. Relevant to the rejected claims, the instant application teaches the analysis of DRB1* genotypes (i.e. each genotype consists of two DRB1* alleles). It is thus unclear from the teachings of the specification what is required for the analysis of 'two different genotypes' in the required identification of a 'patient's genotype for a DRB1* in an HLA class II type gene' (as recited in the first active process step of the claimed method), and further unclear how any one patient may have 'combinations of the same genotype'.

Claim Rejections - 35 USC § 112 - Enablement

3. Claim 1 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not provide for a method in which the caries risk can be determined through the identification of the genotype of DRB1* in a class II type of a HLA gene group wherein genotypes correlating to caries risk have been derived from an antibody titer of immunoglobulin A in human saliva against an antigen of SEQ ID NO: 1.

Nature of the Invention and Breadth of the Claims

Claim 1 is drawn to a method for determining the caries risk in a patient. The method comprises identifying the genotype of DRB1 in a class II type of a HLA gene group, and comparing the genotype with a previously determined caries risk as determined by an antibody titer against an antigen consisting of SEQ ID NO: 1.

Claim 1 encompasses identifying the caries risk in any animal subject, and also includes the analysis of any possible DRB1 genotype as it may be indicative of increased or decreased caries risk. The claim additionally includes any method in which the antibody titer of a secretory immunoglobulin A from saliva in humans is determined using SEQ ID NO: 1 as an antigen, and comparing this antibody value to the identified genotype.

The nature of the invention thus requires knowledge of an association between the caries risk of an individual and DRB1 genotype, and a correlation between a DRB1 genotype, antibody titer of secretory immunoglobulin A to a SEQ ID NO: 1 antigen, and caries risk.

State of the Prior Art, Level of Skill, and Level of Unpredictability

The prior art concerning to the investigation of HLA-DRB1 genotypes and phenotype teaches the examination of particular genotypes with regard to several

diseases that involve immune system components. Though the level of skill with regard to identification of different HLA-DRB1 genotypes in humans is high, results from attempts to demonstrate an association between any particular genotype and a disease state are indicative of an even higher level of unpredictability. Some of the unpredictability in correlating HLA-DRB1 genotype to disease predisposition is due to the highly polymorphic nature of the gene. Epplen et al (1997a) teaches the extremely polymorphic nature of HLA-DRB1, and indicates that DRB1 is the most polymorphic protein-coding locus in man and all vertebrates (p.399 – Abstract).

Acton et al (1999) exemplifies the unpredictable nature of this art. Acton et al reports (p.984 – Abstract; p.988, left col., last ¶) no significant associations were observed between and DRB1 allele and the DMFS index (a measure of caries risk), and further indicates that an association between dental caries and DRB1 alleles was not observed by investigators who assessed military recruits from the Netherlands (p.988, left col., last ¶). and Ozawa et al (2001) teach the determination of an association between MHC alleles and the caries risk. Additionally, the prior art of Ozawa et al (2001) indicates that in an analysis of HLA-DRB1 alleles, no allele frequencies showed significant differences between a caries-free group and a caries-susceptible group (Page 2 – Abstract). Similarly, the post filing art of Chiba et al (2005) demonstrates the difficulty in correlating DRB1 alleles with caries risk. Chiba et al teaches that it is not predictable which DRB1 alleles will be associated with levels of cariogenic bacteria, or cariogenic bacteria levels as stratified by caries-resistant versus caries-susceptible

subgroups. No prior art teaches reliable association between DRB1 genotpye, caries risk, and any antibody titer.

Epplen et al (1997b) teaches the analysis of HLA-DRB1 genotypes in attempts to determine predisposition to multiple sclerosis (MS), early onset pauciarticular arthritis (EOPA) and rheumatoid arthritis (RA). The reference teaches the complex nature of using HLA-DRB1 genotypes as indicators of disease predisposition, and shows that it is often necessary to examine other genetic factors in addition to HLA-DRB1 genotype (Fig4; p.1583 – HLA and disease association: functional aspects vs. linkage disequilibrium). In the examination of MS predisposition, the reference teaches the analysis of more than 600 MS patients and the respective number of controls (p.1582, right column, l.21). The reference further teaches that while DRB*15 correlates with an increased risk of MS, the increased risk of DRB1*03 individuals is hardly recognizable (p.1582, right column, l.31). However, when the DRB1*03 allele is found together with a certain allele of another gene (TCRBV6S3), the risk of developing MS increases 22-fold (p.1583, left column, l.1).

Wyand et al (2000) teaches the use of HLA-DRB1 alleles as predictive indicators of RA. The reference indicates that different alleles (alone and in combination) have been associated with different forms of the disease (p.214, left column, l.7); but the reference also indicates that showing an association between an allele and a phenotype is not necessarily a sign of the extent to which a polymorphism can be used as a biomarker to predict disease course (p.214, left column, l.20). The reference further teaches that proper analysis of the association between HLA allele and disease

requires sufficient patient numbers to control for disease and treatment variables, and to assess the impact of polymorphisms and gene dosing (p.214, left column, l.21).

Walkyria et al (2001) teaches the analysis of HLA alleles with regard to type 1 diabetes in a Brazilian population. The study concludes that there are several haplotypes which include specific DRB1 alleles that occur with increased frequencies in patient groups, as well as a particular DRB1 genotype which correlated to the highest risk for type I diabetes (p.1226 – Abstract). To reach these conclusions, the study utilized a case-control analysis of 181 individuals, which included 70 patients and 111 healthy subjects, in which multiple genes were simultaneously analyzed (p.1227 – Subjects, HLA typing). The conclusion that DRB1*03 and DRB1*04 alleles are indicators of type 1 diabetes susceptibility are drawn from the statistical analysis of the occurrence of these alleles in multiple patients versus controls (p.1229 – predisposing and protective alleles; p.1230 – Table 2). However, pointing to the unpredictability of the utility of DRB1*401 as a susceptibility marker, the reference teaches that the effect of DRB1*401 is variable depending on the population studied (p.1231, left column, l.14). The reference also points out the unpredictability of the effect of different alleles in different populations when teaching the lack of a protective effect of a haplotype that includes DRB1*1501 in the Brazilian population, indicating that such a haplotype usually confers a dominant protective effect in most populations; and that although the population under study was small, the DRB1*1501-containing haplotype was found in two diabetic patients (p.1232, left column, l.5).

Collectively, these studies teach the requirements that enable the determination of an association between a DRB1 allele and a phenotype. Such a determination requires a case-control study with a population large enough to allow a statistically significant analysis of the data. The studies also show the importance of examining other genes (e.g. establishing haplotypes) when investigating DRB1-phenotype associations. Importantly, the studies show that given the enormous number of DRB1 alleles, not every allele will be predictive. Determining an association requires finding a particular allele multiple times in affected or control subjects, and it is a preponderance of alleles in a particular group, not just a single instance of an allele in a single subject, which serves as the basis of the determination.

Amount of Direction Provided and Working Examples

The instant application provides no working example of the use of the claimed method for examination of the caries risk. Furthermore, the specification does not provide any analysis or evidence suggesting a reliable predictive relationship between HLA DRB1 alleles and caries risk. As noted previously in the rejection, knowledge of such a relationship is essential for the practice of the claimed invention.

The specification of the instant application provides an example (p.13 – Example 1) in which DRB1* genotypes and anti-PAC antibodies were analyzed. The specification teaches the determination of HLA-DRB1 genotype via a PCR-RFLP method. The specification teaches the use of several primers (p14-15) for DRB1 amplification:

Primers	Alleles amplified
DR3 and AmpB	DRB1*03, 08, 11, 12, 13, 14

DR4-like and AmpB DRB1*1122, 1410, 1130

The specification does not specifically describe the use of any other primers for the amplification of any other HLA-DRB1 alleles. The specification further describes the treatment of the amplified DRB1 fragments with restriction enzymes, but does not indicate what type of restriction pattern is indicative of any particular genotype.

The specification also teaches the measurement of secretory anti-PAc antibodies in human saliva. The specification teaches an ELISA assay (p.17) in which a PAc peptide, corresponding to amino acids 361-386 of the S. mutans PAc protein, is used as an antigen, and alkaline phosphatase-labeled anti-human IgA is used to detect to detect anti-PAc antibodies. The specification teaches that a high level of anti-PAc antibodies is indicative of a low caries risk (p.11 l.4).

The specification teaches the comparison of HLA-DRB1 genotypes and anti-PAc antibody levels in the saliva of five individuals (p.20 and Table 1). However, the specification teaches that the five individuals (each of which were placed into one of two groups: High antibody value and Low antibody value) all have unique DRB1 alleles. There is no statistical analysis of the data, and in fact the results indicate that no particular genotype is found in more than one individual within either the High versus Low antibody groups, or within the entire population studied; there is no repeated finding of any particular genotype that would lead one to believe that such a genotype would indicated a predisposition or susceptibility for developing caries. In fact, the example provided in the instant specification does not indicate there exists any

correlation between any HLA-DRB1 genotype and antibody levels or caries risk. Furthermore, there is no validation of the predictive use of DRB1 genotypes in examining caries risk, nor any analysis of whether or not the individuals in the study actually developed caries.

Quantity of Experimentation Needed to Use the Invention

The quantity of experimentation required to use the claimed invention is high. If one wished to use the methods outlined in the instant specification to determine caries risk, one would first have to conduct a larger scale case-control study to discover which DRB1 alleles are present in caries-sensitive subjects versus subjects resistant to caries. Such a study may be focused on a general population or a specific subpopulation (e.g.: ethnic or geographic), and may also include corrections for environmental factors such as diet or hygiene. Such a study would have to be large enough in scope to detect correlations between any of the many different DRB1 alleles and a risk of caries; as the specification indicates, solving all combinations of DRB1 dimers would allow for accurate evaluation of the caries risk (though the instant specification provides information about DRB1 alleles from only five individuals). One would also have to analyze any possible genotype as it relates to antibody titer of immunoglobulin A against the antigen consisting of SEQ ID NO: 1 and further establish that antibody titer is indicative of caries risk. Validation of any specific alleles alleged to be useful for prediction of an increased caries risk would have to go beyond just showing a correlation with increased antibodies or higher levels of S. mutans in the oral cavity, and have to show an actual correlation with increased caries development.

Conclusion

Taking into consideration the factors outlined above, including the nature of the invention and scope of the claims, the state of the art and its high level of unpredictability, the lack of guidance by the applicant and the lack of a working example, it is the conclusion the an undue amount of experimentation would be required to use the invention as claimed.

Response to Remarks

4. Applicants have traversed the rejection of claims under 35 USC 112 1st ¶ for lack of enablement. Applicants argue (p.6-7 of the Remarks) that the method requires that a table be prepared that correlates genotypes at the DRB*1 locus to the antibody titer, as exemplified in the specification, and thus the inventors have shown that it is possible to determine caries risk through genotyping analysis. This argument is not found to be persuasive. From an enablement perspective, an artisan of skill would have to be able to predict the association between multiple parameters: between caries risk and antibody titer, and also between antibody titer and DRB*1 genotype, such that identification of any DRB1* genotype is indicative of any antibody. In the instant case, the examples of the specification and the teachings of the prior art and post-filing art demonstrate the unpredictability of reliably associating any of these factors and therefore an artisan of skill would require extensive experimentation as discussed above to practice the claimed invention.

Considering the first required association (i.e. between antibody titer and caries risk), it is noted that neither the instant application nor the art of record demonstrates

any statistically significant correlation between antibody titer and caries risk, rather the art of record emphasizes that such a relationship is not predictable. In fact the instant specification provides no analysis of any level of caries risk in any patient. The specification shows only that in an analysis of five individual patients, each patient has a different titer of anti-Pac peptide antibody. There is no correlation, however, between this particular antibody titer and caries risk. This is particularly relevant considering that the prior art does not teach any reliable association between any particular level of any antibody and the risk of caries.

Considering the second required association (i.e. between DRB1* genotype and antibody titer), as addressed in the rejection, the instant specification only demonstrates the analysis of the DRB1* genotypes of five individuals where the antibody titer of the individual is known (Table 1 page 21 of specification). The specification provides no analysis of the data with regard to any consistent significant association between those genotypes and the antibody titer in any other individuals. It is highly unpredictable, as argued by Applicants and required by the claimed method, whether or not, for example, the 0403/0405 DRB1* genotype would be indicative of a high anti-Pac peptide antibody titer in every individual patient the same way patient A in the specification has the aforementioned genotype and also has a high antibody titer.

While applicants argue that one can correlate the antibody titer and genotype, and use this correlation to define the caries risk (p.6 of Remarks), the Examiner maintains that the instant disclosure merely provides the analysis of antibody titer and DRB1* genotypes in several individuals, and does not provide that there is any

significant, consistent, or general correlation of genotype with antibody titer, such that such a correlation is indicative of caries risk. Further, as required by the claimed method, the instant specification does not provide for any significant or consistent correlation between any particular level of antibody titer and a specific caries risk, where such an association is required for the claimed methods.

The rejection as set forth is **MAINTAINED**.

Withdrawn Claim Rejections - 35 USC § 103

5. Applicants have traversed the rejection of claims under 35 USC 103 as obvious in view of the teachings of the prior art. Applicants' argument (p.4 of Remarks) that Acton et al does not teach an association between DRB genotypes and high caries risk is persuasive. Acton et al reports (p.984 – Abstract; p.988, left col., last ¶) no significant associations were observed between and DRB1 allele and the DMFS index (a measure of caries risk), further indicating an association between dental caries and DRB1 alleles was also not observed by investigators who assessed military recruits from the Netherlands (p.988, left col., last ¶). These issues are addressed in the rejection of claims for lack of enablement.

The rejection is **WITHDRAWN**.

Conclusion

6. No claim is allowed

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Kapushoc whose telephone number is 571-272-3312. The examiner can normally be reached on Monday through Friday, from 8am until 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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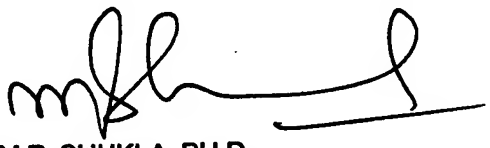
Stephen Kapushoc
Art Unit 1634



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